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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 02/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/996,507	WANG, LAIXIN	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *05 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *28 November 2001* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 2/2/02, 8/18/03
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 11/5/03. Applicants election without traverse of PEI, synthetic or natural polypeptide ligands, streptolysin O, and a polypeptide linker is acknowledged.

Claims 1-64 are under consideration in this Office Action.

The polycationic polymer species "polylysine" is disclosed by Schacht et al (see rejections under 35 USC 102 below), and is hereby rejoined.

Information Disclosure Statement

Information Disclosure Statements were received and entered on 8/18/03 and 2/20/02.

Claim Objections

Claim 17 is objected to for lack of subject-verb agreement. The second instance of "is" should be "are".

Claims 30 and 56 are objected to because the recited tetrapeptides are not identified by SEQ ID NO. Insertion of "(SEQ ID NO:2)" after the first tetrapeptide, and insertion of "(SEQ ID NO:1)" after the second tetrapeptide is suggested.

Claim 48 is objected to because the second instance of "polymer" should be plural.

Drawings

Applicant has submitted drawings which are accepted for the purpose of examination.

Claim Rejections - 35 USC § 112

Claims 1-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods and carriers for transporting polyanionic macromolecules across a cellular membrane, does not reasonably provide enablement for methods and carriers for transporting polyanionic macromolecules across cellular biological barriers other than membranes, as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-47 are drawn to compositions with an intended use of transporting a polyanionic macromolecule across a biological barrier of a cell. Claims 48-64 are drawn to methods of transporting a polyanionic macromolecule across a biological barrier of a cell. The specification focuses on the delivery of nucleic acids complexed with polycations, wherein the polycations are covalently attached to a hydrophilic polymer such as PEG or HPMA. The aim of the invention is to decrease the toxicity of polycation/nucleic acid complexes, increase their stability in serum, and improve their dissociation within a target cell. See page 4, lines 13-21.

In view of the specification at page 5, line 5, and page 7, line 18, the scope of biological barriers of a cell includes cell walls, particularly plant cell walls.

The specification provides no guidance regarding delivery of polyanionic macromolecules across any biological barrier other than the cell membrane, endosomal membranes, and nuclear membranes.

A review of the prior art indicates that polycations may be used to augment transfection of plant cells, but these procedures require the formation of protoplasts, i.e. removal of the plant cell wall, prior to transfection with nucleic acid/polycation complexes. See e.g. Antonelli et al (Theoretical and Applied Genetics (1990 80(3): 395-401). In order to transfer nucleic acids to plant cells without removal of cell walls, those of skill in the art generally use agrobacterium- or particle bombardment-mediated approaches. See e.g. Taylor et al (DNA and Cell Biol. 21(12): 963-977 (2002)), especially page 964 column 1, second full paragraph through paragraph bridging columns 1 and 2. The specification does not contemplate or provide any guidance regarding the combination the instant methods and compositions with agrobacterium-, particle bombardment-mediated, or any other mode of delivery. In view of the teachings of the prior art that indicate that polycation/DNA complexes are delivered to plant cells only after the cell wall has been removed, the state of the art regarding delivering nucleic acids to cell wall-containing plant cells, and the failure of the specification to provide any specific guidance relating to the delivery of nucleic acids through cell walls, one of skill in the art would have to perform undue experimentation in order to use the claimed invention for this intended purpose.

This rejection can be overcome by substituting "membrane" for "biological barrier" in the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8, 12-16, 20, 21, 38-40, 57-59, and 61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 is indefinite because it does not end in a period.

Claims 12-16, 20, 21, 38-40, 57-59, and 61 are indefinite because they recite molecular weights, but do not give units of weight or mass.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7, 9-15, 17, 20, 22-25, 27, 30-39, 41-44, 48-51, 53-58, 60, and 61 are rejected under 35 U.S.C. 102(b) as being anticipated by Schacht et al (WO 98/19710, published 5/14/98).

Schacht teaches synthetic polymer-based carrier vehicles for nucleic acid delivery to cells, and methods of use. Complexes of nucleic acid and polycations such

as PEI are formed, and then hydrophilic polymers are used to cross link the polycations. See e.g. abstract, page 3, lines 1-31, and Fig. 1. The hydrophilic polymer may be PEG or HPMA. See page 6, lines 18-24; page 9, lines 28-35, and page 25, lines 25 and 26. The polycation may be polyethyleneimine, polylysine or polyallylamine, etc. See page 25, lines 28 and 29. The compositions may comprise cell polypeptide targeting moieties and membrane disrupting agents such as fusogenic peptides. These agents and moieties may be linked to either the polycation or the hydrophilic polymer. See page 4, lines 10-26; page 6, lines 3-17; page 19, lines 14-19; and paragraph bridging pages 46 and 47. The hydrophilic polymers and polycations may be linked by peptide linkers comprising the sequence GlyPheLeuGly. See paragraph bridging pages 10 and 11. the molecular weight of the hydrophilic polymer may be about 20,000 Da. See page 14, lines 28-30. The molecular weight of the polycation may be 3-2 kDa. See page 10, lines 9-17. the nucleic acid may be plasmid DNA, RNA, ribozyme, or antisense oligonucleotide. See e.g. page 10, lines 1-3, and claim 42 at page 57.

Thus Schacht anticipates the claims.

It is noted that US Patent 6,312,727 is a continuation of WO/98/19710, discloses all of the information set forth therein.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 17, 18, 19, 28, 29, 31, 46, 47, 48, 63, and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schacht et al (WO 98/19710, published 5/14/98).

The teachings of Schacht are reviewed above. Briefly Schacht teaches complexes and methods for delivering polyanionic molecules to cells. The complexes comprise polycations bound to the nucleic acid, and crosslinked with a hydrophilic polymer.

Schact teaches that the hydrophilic polymer is multivalent and has more than one reactive group for crosslinking to the polycationic polymer. While Schact does not explicitly teach that more than two polycationic polymers are crosslinked by a given hydrophilic polymer, Schact does teach at column 6, lines 27-60 that crosslinking of polycatinic polymers with a ydrophilic polymer can stabilize the polycation/nucleic acid complex. It wold have been obvious to one of ordinary skill in the art at the time of the invention to cross link polycations with hydrophilic polymers as taught by Schact. The number of crosslinkages between the polycations and the hydrophilic polymers is considered to be a matter of design choice that affects the stability of the complex, and would be routinely optimized by one of ordinary skill in the art. Absent evidence of unexpected results, formation of complexes having 8-15 polycations crosslinked by a hydrophilic polymer is considered to be obvious.

Thus the invention as a whole was prima facie obvious.

Claims 1, 7, 8, 17, 25, 26, 31, 45, 48, and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schacht et al (WO 98/19710, published 5/14/98) in view of Bayley et al (US Patent 5,777,078, issued 7/7/98).

The teachings of Schacht are reviewed above. Briefly Schacht teaches complexes and methods for delivering polyanionic molecules to cells. The complexes comprise polycations bound to the nucleic acid, and crosslinked with a hydrophilic polymer. The complexes may comprise lytic peptides that degrade membranes, thereby allowing delivery of the nucleic acids. See page 4, lines 20-24; page 19, lines 14-19; and page 47, lines 6-12.

Schacht does not teach the use of streptolysin O as a lysis agent.

Bayley teaches compositions for improving DNA uptake into cells, comprising a lytic agent attached to a targeting ligand. The lytic agent may be streptolysin O. See column 1, lines 47-59 and column 2, lines 13-21.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use as a lytic agent in the invention of Schacht streptolysin O. One would have been motivated to do so because Bayley teaches that streptolysin O is useful for forming pores in membranes to allow delivery of nucleic acids.

Thus the invention as a whole was prima facie obvious.

Claims 1, 16, 17, 21, 31, 38-40, 48, 57, 59, 60, and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schacht et al (WO 98/19710, published 5/14/98) in view of Wagner et al (US 2001/0005717, published 6/28/01).

The teachings of Schacht are reviewed above. Briefly Schacht teaches complexes and methods for delivering polyanionic molecules to cells. The complexes comprise polycations bound to the nucleic acid, and crosslinked with a hydrophilic polymer. Schacht does not teach polycations in the range of 400-2000 Da.

Wagner teaches complexes of PEI and nucleic acids wherein the PEI is modified with a hydrophilic polymer. The PEI may have a molecular weight in the range of 700-2,000,000 Da. See paragraph 20 on page 2.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use PEI of molecular weight 700 in the invention of Schacht. One would have been motivated to do so because Wagner teaches that smaller PEI molecules are less toxic. See paragraph 20 on page 2.

Thus the invention as a whole was prima facie obvious.

Claims 31, 32, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schacht et al (WO 98/19710, published 5/14/98) in view of Boggs et al (US Patent 5,681,747, issued 10/28/97).

The teachings of Schacht are reviewed above. Briefly Schacht teaches complexes and methods for delivering polyanionic molecules to cells. The complexes comprise polycations bound to the nucleic acid, and crosslinked with a hydrophilic polymer. Schacht does not teach chimeric RNA/DNA oligos, phosphorothioate oligos, 2'-O-methyl oligos, PNAs or morpholino conjugates.

Boggs teaches protein kinase C antisense oligonucleotides that may contain chimeric RNA/DNA oligos, phosphorothioate oligos, 2'-O-methyl oligos, PNAs and morpholino conjugates. See paragraph bridging columns 6 and 7.

It would have been obvious to one of ordinary skill in the art at the time of the invention to se the invention of Schacht to deliver teach chimeric RNA/DNA oligos, phosphorothioate oligos, 2'-O-methyl oligos, PNAs or morpholino conjugates, because Boggs teaches that such oligos can be used to inhibit protein kinase C function or as in vivo diagnostic reagents (see abstract and column 8, lines 16-34), and because the compositions of Schacht provide improved stability (see page 3, lines 18-24.

Thus the invention as a whole was prima facie obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at 703-306-3217 before 2/22/04, and at 571-272-0811 after 2/22/04. The official central fax number is 703-872-9306 until further notice. Inquiries of a general nature or relating to the status of the application should

be directed to the Patent Analyst Trina Turner whose telephone number is 571-272-0564.

DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.